National Toxicology Program
Toxicity Report Series
Number 20

NTP Technical Report
on Toxicity Studies of

Diethanolamine

(CAS No. 111-42-2)

Administered Topically and in Drinking Water
to F344/N Rats and B6C3F$_1$ Mice

Ronald L. Melnick, PhD, Study Scientist
National Toxicology Program
Post Office Box 12233
Research Triangle Park, NC 27709

NIH Publication No. 92-3343
October 1992

United States Department of Health and Human Services
Public Health Service
National Institutes of Health

CONTRIBUTORS

The NTP report on the toxicity studies of diethanolamine is based primarily on 2- and 13-week studies that began in October, 1986, and ended in January, 1988, at Battelle Memorial Laboratories, Columbus, OH.

National Toxicology Program
Evaluated experiment, interpreted results, and reported findings

Ronald L. Melnick, PhD
Study Scientist
John R. Bucher, PhD
Leo T. Burka, PhD
Rajendra S. Chhabra, PhD
Michael P. Dieter, PhD
Michael R. Elwell, DVM, PhD
Joel F. Mahler, DVM
Robert R. Maronpot, DVM
H.B. Matthews, PhD
Morrow B. Thompson, DVM, PhD
Errol Zeiger, PhD

Coordinated report preparation

Jane M. Lambert, BS
Edison McIntyre, BS
Diane Overstreet, BS
Kristine Witt, MS
Oak Ridge Associated Universities

NTP Pathology Working Group
Evaluated slides and prepared pathology report

John Seely, DVM
Chairperson
PATHCO
Michael R. Elwell, DVM, PhD
National Toxicology Program
Katharina Heider, DVM
Ciba-Geigy
Joel Leininger, DVM, PhD
National Toxicology Program
Margarita McDonald, DVM, PhD
National Toxicology Program
John Peckham, DVM, MS, PhD
Experimental Pathology Laboratories, Inc.
Gary Riley, MVSc, PhD
Experimental Pathology Laboratories, Inc.

Battelle Memorial Labs, Columbus, OH
Principal contributors

Milton Hejtmancik, PhD
Arthur C. Peters, PhD
Allen Singer, DVM
Larry Mezza, DVM
Ronald Persing, DVM
Michael Ryan, DVM, PhD

Research Triangle Institute
Conducted disposition studies

R. Jeffcoat, PhD
Principal Investigator
D. Feldman, DVM
Study Veterinarian
J. Haw
Quality Assurance
J. Mathews, PhD
Study Director
M. Parker
Chemist
T. Tippin
Chemist

Experimental Pathology Laboratories, Inc.
Performed pathology quality assurance

William F. MacKenzie, DVM, MS

Experimental Health Research and Testing Inc.
Performed sperm morphology and vagina cytology evaluation

D. Bailey

Analytical Sciences, Inc.
Performed statistical analysis

Steven Seilkop, MS
Janet Teague, MS

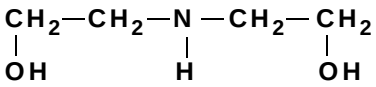
TABLE OF CONTENTS

FIGURES

PLATES

APPENDICES

Diethanolamine



Molecular formula: $C_4H_{11}NO_2$
CAS Number: 111-42-2 **Molecular Weight**: 105.14
Synonyms: 2,2'-iminodiethanol; 2,2'-iminobisethanol; diethylolamine; bis(hydroxyethyl)amine; 2,2'dihydroxydiethylamine; 2,2'-aminodiethanol

ABSTRACT

Diethanolamine is a high-production chemical used in cosmetics, in cutting fluids, as a dispersing agent for agricultural chemicals, and as an absorbent for acidic gases. Toxicology studies of diethanolamine were conducted in F344/N rats and B6C3F$_1$ mice of both sexes for 2 weeks (5/sex/species/dose) and 13 weeks (10/sex/species/dose) to characterize and compare the effects of oral and dermal exposure. In addition to histopathology, evaluations included clinical pathology, urinalyses, and sperm morphology or vaginal cytology. *In vitro* genetic toxicity studies included assessments of mutagenicity in *Salmonella typhimurium* and mouse lymphoma L5178Y cells, analysis of chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells, and determination of micronuclei formed in mice during the 13-week dermal exposure study.

Groups of rats and mice received drinking water containing diethanolamine at concentrations of up to 10000 ppm during studies of 2 or 13 weeks duration. In the 2-week studies, rats and mice of both sexes received in the were 0, 630, 1250, 5000, and 10000 ppm diethanolamine in the drinking water. In the 13-week studies, rats received 0, 320, 630, 1250, 2500, and 5000 ppm (males) or 0, 160, 320, 630, 1250, and 2500 ppm (females) in drinking water; male and female mice received 0, 630, 1250, 2500, 5000, and 10000 ppm. All female rats in the 2 highest dose groups and 2 males in the 10000 ppm group in the 2-week study died before the end of the study. In the 13-week study, deaths of mice occurred in the 3 highest dose groups; 2 male rats in the top dose group also died. Surviving animals in the higher concentration groups in both studies exhibited depressed weight gains. Rats receiving diethanolamine developed a poorly regenerative, microcytic anemia in both studies. In the 2-week study, dosed male and female rats had increased kidney weights, renal tubular cell necrosis, and decreased renal function; rats in the 13-week study also showed increased incidences or severity of nephropathy, tubular necrosis, and mineralization. Degeneration of the seminiferous tubules of the testis was noted in dosed males in both the 2- and 13-week studies, and sperm motility and count were decreased in the 13-week study. Demyelination in the brain (medulla oblongata) and spinal cord was observed in male and female rats in the 13-week study. In mice, dose-dependent increases in liver weight were observed in males and females in the 2-week study; cytologic alteration and

necrosis of individual hepatocytes were observed in the highest dose group. In the 13-week drinking water study in mice, nephropathy and tubular necrosis were observed in males, and degeneration of cardiac myocytes, and hepatocellular necrosis were seen in males and females. Cytologic alteration in the submandibular salivary gland was noted in male and female mice. Hepatocyte cytologic alteration also was noted in all dosed groups of mice.

In the 2-week dermal studies, groups of rats and mice were administered daily doses of diethanolamine in 95% ethanol, ranging from 160 to 2500 mg/kg for mice, and from 125 to 2000 mg/kg for rats, 5 days per week. In 13-week studies, dermal doses ranged from 32 to 500 mg/kg for rats, and from 80 to 1250 mg/kg for mice. In the 2-week study, early deaths of male rats and male and female mice occurred in the highest dose groups and in female rats in the 2 highest dose groups (1000 and 2000 mg/kg). Body weight gains were reduced in rats and mice in the higher dose groups. Early deaths in the 13-week study were observed in the highest dose groups of rats (500 mg/kg) and mice (1250 mg/kg). Body weight gains were reduced in rats and mice given the higher doses. Rats in the dermal studies exhibited dose-dependent hematologic and renal function changes similar to those observed in rats in the drinking water study. In addition, in the 2-week study, rats exhibited ulcerative skin lesions at the site of application, accompanied by inflammatory cell infiltration, hyperkeratosis, and acanthosis (hyperplasia) of the epidermis. Hyperkeratosis, without ulceration, was observed in some animals. Ulceration at the site of application was observed in male and female mice. Acanthosis, without ulceration or inflammatory cell infiltration, was observed in mice in all lower dose groups. In the 13-week study, skin lesions at the site of application included ulceration and inflammation, hyperkeratosis, and acanthosis. Liver weights were increased in male and female rats, but there were no associated histopathological changes. Other treatment-related effects observed in rats included demyelination in the brain and spinal cord, and nephropathy, renal tubular necrosis, and/or tubular mineralization; mice exhibited cytological alterations in the liver and/or hepatocellular necrosis, renal tubular epithelial necrosis, and cardiac myocyte degeneration.

In *in vitro* genetic toxicity studies, diethanolamine was not mutagenic in *Salmonella typhimurium* or mouse L5178Y $TK^{+/-}$ cells. Diethanolamine did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells, nor did it induce micronuclei in peripheral blood erythrocytes in mice exposed by topical application for 13 weeks. All *in vitro* studies were conducted with and without S9 activation.

Target organs of diethanolamine toxicity identified in these studies included bone marrow, kidney, brain, spinal cord, testis, and skin in rats, and liver, kidney, heart, salivary gland, and skin in mice. A no-observed-adverse-effect-level (NOAEL) was not achieved for hematological changes or nephropathy in rats (< 160 ppm), or for cytologic alteration of the liver in mice (< 630 ppm) in the drinking water studies. In the dermal studies, a NOAEL was not achieved for hematological changes, nephropathy, or hyperkeratosis of the skin in rats (< 32 mg/kg), or for cytologic alteration of the liver or acanthosis of the skin in mice (< 80 mg/kg).

PEER REVIEW

Peer Review Panel

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies on diethanolamine on November 21, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine if the design and conditions of the NTP studies are appropriate and to ensure that the toxicity study report presents the experimental results and conclusions fully and clearly.

National Toxicology Program's Board of Scientific Counselors Technical Reports Review Subcommittee

Paul T. Bailey, PhD
Mobil Oil Corporation
Toxicology Division
Princeton, NJ

Louis S. Beliczky, MS, MPH
Department of Industrial Hygiene
United Rubber Workers Intl. Union
87 South High Street
Akron, OH

Gary P. Carlson, PhD
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Kowetha A. Davidson, PhD
Health and Safety Research Division
Oak Ridge National Laboratory
Oak Ridge, TN

Harold Davis, DVM, PhD
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, DVM
Consultants in Veterinary Pathology
Murrysville, PA

Jay I. Goodman, PhD
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

David W. Hayden, DVM, PhD
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

Curtis D. Klaassen, PhD (Chair)
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

* Daniel S. Longnecker, MD
Department of Pathology
Dartmouth Medical School
Hanover, NH

Barbara McKnight, PhD
Department of Biostatistics
University of Washington
Seattle, WA

* Ellen K. Silbergeld, PhD
University of Maryland Medical School
Baltimore, MD

Matthew J. van Zwieten, DVM, PhD
Senior Director, Safety Assessment
Merck, Sharpe, and Dohme Research Labs.
West Point, PA

Lauren Zeise, PhD
California Department of Health Services
Berkeley, CA

* Unable to attend meeting.

Summary of Peer Review Comments

Dr. R.L. Melnick, NIEHS, introduced the short-term toxicity studies of diethanolamine by reviewing the uses, experimental design, and results.

Dr. Carlson, a principal reviewer, said this was a well-written report. He questioned the statement that a NOAEL was not achieved for female mice in the dermal studies, commenting that 80 mg/kg appeared to be a NOAEL based on lack of cytologic alteration of the liver. Dr. Melnick agreed but pointed out that 80 mg/kg was not a NOAEL for dermal lesions. Dr. Carlson thought that while perhaps statistically correct, it seemed to be stretching a point to say that a NOAEL was not observed in the rat based on hematologic studies when the change was 1 percent or less.

Dr. Garman, a second principal reviewer, agreed that this was a very well-written, thorough, and well-documented report. He noted that, although there were neurologic signs in rats on the 2-week water studies, neuropathologic changes were not noted until 13 weeks and wondered if additional stains might be warranted to be sure the clinical signs were not indicative of early neuropathologic changes. Dr. J.F. Mahler, NIEHS, responded that the brain sections from the 2-week studies were reviewed with particular attention to the same areas that were affected in the 13-week studies, and no lesions were observed. Dr. Garman asked that more precise neuroanatomic locations be stated in photomicrographs of brain lesions.

Dr. Bailey commented that there had been extensive, long-time use of diethanolamine and related amines in industry, primarily in formulations, and that corresponding subchronic testing has been done. He said he was unaware of findings of neurologic and testicular toxicity. He suggested that the NTP might want to solicit information on these studies, many of which would be unpublished.

Seeing no objections, Dr. Klaassen accepted the report with the suggested editorial and other changes on behalf of the panel.